

Full Length Research Paper

The epidemiology of congenital heart diseases in Saudi Arabia: A systematic review

Amirah M. Alenezi¹, Nada M Albawardi², Anna Ali³, Mowafa S. Househ⁴ and Ashraf Elmetwally^{3*}

¹King Abdulaziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia.

²Prince Sultan Center for Special Education Support Services. Riyadh, Saudi Arabia.

³Department of Epidemiology and Biostatistics, College of Public Health and Health Informatics, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

⁴Department of Health informatics, Collage of Public Health and Health Informatics, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

Received 9 March, 2015; Accepted 4 June, 2015

Several studies have been conducted on congenital heart disease in different regions of Saudi Arabia. However, no recent systematic review has examined the growing scientific evidence with respect to the epidemiology of CHD in the Kingdom. The aim of this review is to provide a comprehensive summary of CHD incidence, prevalence, burden and impact on the Saudi population. A literature search was conducted through PubMed and Google Scholar using relevant keywords to identify studies performed in Saudi Arabia regarding CHD from 1993 to December 2013. Articles written in English that described or investigated the epidemiology, etiology, distribution, impact and burden of CHD in the Saudi Arabian population were included. Twenty one articles met these criteria. Cross-sectional studies found the prevalence of CHD ranging between 2.1 and 10.7 per 1,000 persons. The most prevalent type of CHD was the ventricular septal defect ranging from 29.5 to 39.5% of all diagnosed CHDs, followed by atrial septal defect (8.9 to 18.1%) and pulmonary stenosis (6 to 12.4%). Overall, the incidence of severe CHD was approximately 5.4 per 1,000 live births per year. Occurrence of CHD in Saudi Arabia was significantly associated with Down's syndrome, consanguinity and maternal diabetes. Studies on the burden of these anomalies on children, families and society are scarce. This systematic review found that prevalence of CHD is comparable to that in other developing countries. Several modifiable risk factors have been identified emphasizing the importance of public health programs that are aimed at tackling such potentially preventable risk determinants.

Keywords: Heart, congenital, defect, epidemiology, prevalence, Saudi.

INTRODUCTION

Congenital Heart Disease (CHD) has been defined as “a

gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance” (Mitchell et al., 1971). The range of defects

varies from a single simple defect with no symptoms to multiple complex of defects with several symptoms (Bernier et al., 2010). Minor heart defects may not affect the quality of life of the patient and may not require any intervention; on the other hand, severe heart defects would require extensive medical support (Koshnood et al., 2010; van der Bom et al., 2012). Different studies give wide variation in the incidence of CHD varying from 4/1000 to 50/1000 live births (Hoffman et al., 2004). Variation is primarily due to the use of different methods of diagnosis (Hoffman et al., 2004). The highest prevalence for CHD was observed in a population based study from Taiwan with a prevalence of 13.1 per 1,000 live births between 2000 and 2006 (Wu et al., 2010). In most CHD cases, the etiology is not known, but some studies have found that CHD is linked with either genetic or environmental predispositions (Blue et al., 2012). Several studies have been conducted on CHD in different regions of Saudi Arabia. However, no recent systematic review has examined the growing scientific evidence with respect to the epidemiology of CHD in the Saudi population. The aim of this review is to provide a comprehensive summary of CHD incidence, prevalence, burden and impact on the Saudi population in order to better understand the disease's magnitude and aid in future public health initiatives.

METHODOLOGY

An electronic search was conducted from January 3 to January 25, 2014 using PubMed, Google Scholar and local Saudi journals. The following keywords: "Heart", "Cardiac", "Congenital", "Defect" and "Epidemiology", "Prevalence", "Incidence", "Risk", "Impact", and "Saudi Arabia" were used in the search strategy. The articles included in the study were from Pubmed and local journals, written in English and they describe or investigate the epidemiology, etiology, distribution, impact or burden of CHD in Saudi Arabia. Treatment or interventional studies were excluded. The search identified 108 articles. Titles, abstracts and at a later stage full texts were reviewed independently by two researchers to identify articles that met the predefined inclusion criteria. After mutual consensus of the two researchers 21 articles met the inclusion criteria with publication dates ranging from 1993 to 2013. Figure 1 shows a flow chart of the search with justification for exclusion at each stage. A supplementary search for articles by the primary investigator was conducted by cross-referencing and reviewing locally published journals that were not indexed in PubMed.

RESULTS

The 21 studies included were conducted in a variety of

geographical areas in Saudi Arabia. The supplementary search by cross-referencing and searching in local journals did not identify any additional papers. Of the 21 articles, five reported on prevalence and pattern of CHD and seven reported on the association of CHD with Down's syndrome and its prevalence. Nine studies reported on risk factors only such as consanguinity, maternal diabetes, maternal obesity, the social impact of CHD and fetal outcome (Table 1).

Prevalence and pattern of CHD

A study investigated the clinical features of 320 patients diagnosed with CHD at a Saudi hospital in the period between 1988 and 1991 found that both sexes were equally affected. Relative frequency of VSD was higher than Atrial Septal Defect (ASD), Pulmonary Stenosis (PS), Patent Ductus Arteriosus (PDA) and Atrio-ventricular Septal (AVSD) with percentages of 38.5, 11.5, 9, 8% and 5%, respectively (Jaiyesimi et al., 1993). Bhat et al., (1997) screened all children referred to the cardiology clinic at the Madina Maternity and Children Hospital for three years and documented very similar findings with VSD representing 29.7% of all CHD diagnoses, ASD (26%), PS (16.1%) and PDA (13.2%) (Baht et al., 1997). Abbag (1998) documented that the most common defect was VSD 32.5% (Abbag, 2006). Likewise, Alabdulgader (2001) studied the prevalence of CHD using a cross-sectional design and concluded that VSD was the most common defect (39.5%), followed by ASD (11.5%), PS (8.9%), PDA (8.6%), AVSD (3.5%), Tetralogy of Fallot, TOF (4.2%), Coarctation of Aorta COA (2.7%), Aortic Stenosis (AS) (3.5%) (Alabdulgader, 2001). Few studies estimated the prevalence of CHD at the population level. Greer et al. (2005) showed that Southwestern region had the highest burden of CHD with a period prevalence of 748 cases per 100,000 persons (Greer et al., 2005). Alqurashi et al. (2006) determined the prevalence of CHD in children and adolescents by randomly sampling households in all regions of Saudi Arabia. The results found the prevalence of CHD over all as 21 per 10,000 persons. VSD was the most common defect with 10 cases per 10,000 (Alqurashi et al., 2006). Alnajjar et al., (2009) found that CHD represents 34.4% of all cardiac problems diagnosed at Al Madina city. Ventricular septal defect period represented 34.5% of all CHD diagnoses, followed by ASD (8.9%), PS (7.9%), PDA (6%), AVSD (3.8%), TOF (3%), AS (3.5%), COA (3.4%), Transposition of the Great Arteries (TGA) (3.5%),

*Corresponding author. E-mail: ashraf.elmetwally@gmail.com .Tel: 00966594800755.

Author(s) agree that this article remain permanently open access under the terms of the [Creative Commons Attribution License 4.0 International License](https://creativecommons.org/licenses/by/4.0/)

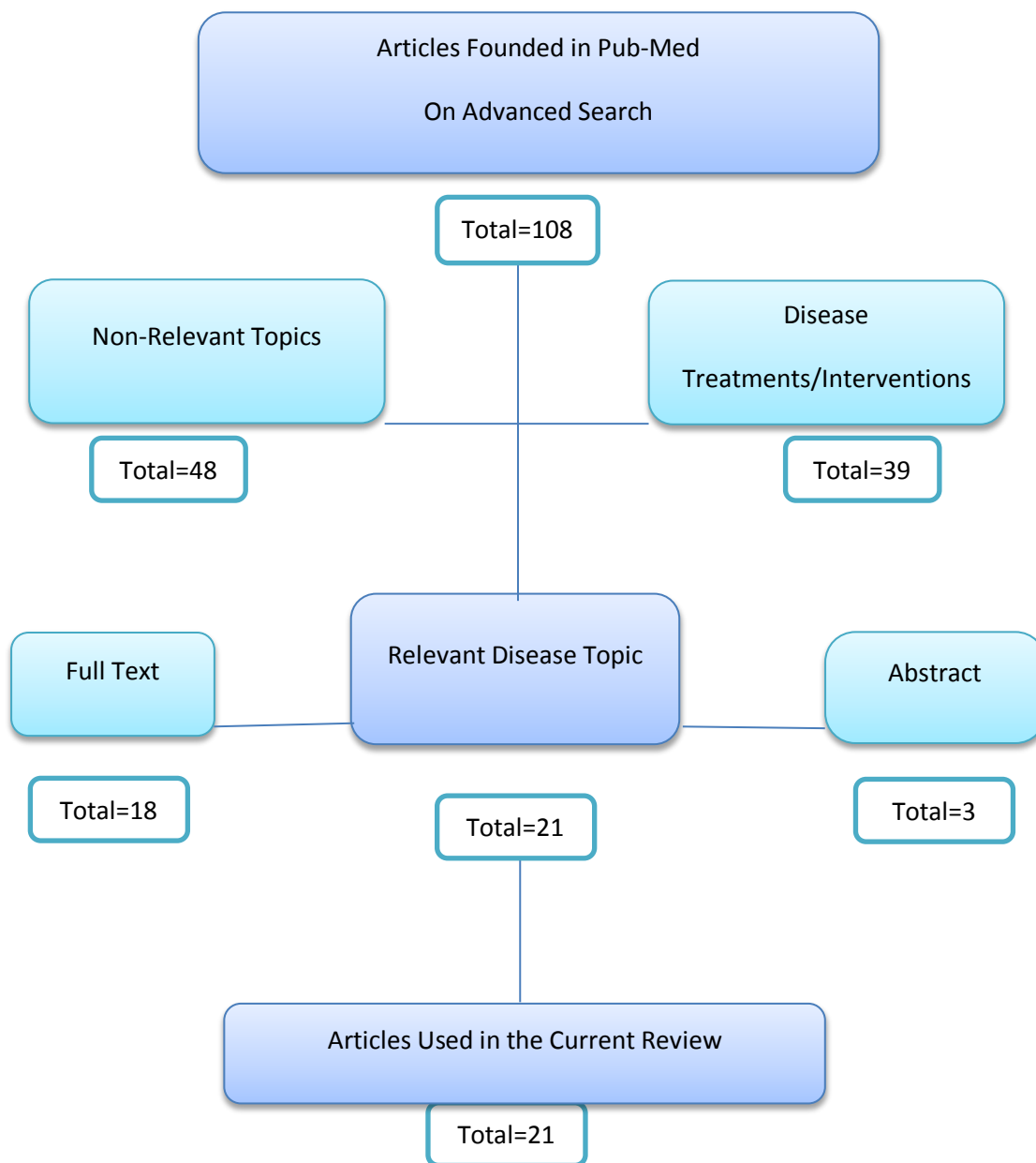


Figure1. Flow chart of the literature review search.

and others (26%) (Alnajjar et al., 2009). Almazini and Al-Ghamdiin (2011) studied the proportion of CHD among all diagnoses in the Southwestern Albaharegion. Of all cardiac patients, 26.8% were diagnosed with CHD (Almazini and Al-Ghamdiin, 2011). Al-Mesned et al., (2012) reported on the incidence of severe CHD in Al-Qassim. The incidence of severe CHD was 5.4/1,000 live births/year. VSD defect was the most common lesion 22.5/1,000 live births/year (Al-Mesned et al., 2012).

Risk factor studies

Down syndrome (DS)

Alabdulgader, (2001), reported that Down syndrome was found in 6% of all patients with CHD. Down syndrome patients with CHD presented with higher proportion of non-cyanotic lesions, than cyanotic lesions (Alabdulgader, 2001). Al-Jarallah (2009) reported a 49%

Table 1. Summary of studies included in the systematic review.

Study	Sample Size	Study setting	Year of data collection	Prevalence/incidence	Other findings
Prevalence/incidence and relative frequency Studies					
Jaiyesimi et al. (1993)	320 cases of CHD	Hospital	1988-1991	-	Relative frequency of VSD was 38.5% followed by ASD (11.5%), PS (9%), PDA (8%) and finally AVSD (5%). A relatively high incidence of trisomy -21 was found in 10%.
Bhat et al. (1997)	1209 CHD cases	Hospital	1992-1995	-	Frequently detected types of CHD were VSD (29.7%) followed by ASD (26%), PS (16.1%) and PDA (13.2%). DS was found in 79% of patients with AVSD
Abbag (1998)	608 cases of CHD	Hospital	1994-1996	-	Relative frequency of VSD (32.5%), followed by PDA (15.8%), ASD (10.4%), PS (10.1%), AVSD (3.6%), TOF (4.5%), AS (2.7%), COA (2.7%), and TGA (1.5%)
Greer et al. (2005)	5,865 cases of CHD	National Registry	1998-2002	748/100,000	The southwestern region having the highest burden of CHD
Alqurashi et al. (2007)	95 cases of CHD	Household	2004-2005	21/10,000	The Central region had the highest prevalence with 27 cases per 10,000 persons; the Northern and Eastern region had prevalence of 25 cases per 10,000 persons each, and Southwestern Region prevalence of 21 cases per 10,000 persons. The VSD was the most common defect with 10 cases per 10,000
Alnajjar et al. (2009)	4348 cases of CHD	Hospital	2007-2208	-	Relative frequency of VSD 34.5%, followed by ASD (8.9%), PS (7.9%), PDA (6%), AVSD (3.8%), TOF (3%), AS (3.5%), COA (3.4%), TGA (3.5%), and others (26%)
Almawazini et al. (2011)	2610 cases of CHD	Hospital	2005-2010	-	VSD (29.6%), PDA (9.5%), ASD (9.3%), PS (7.9%), AVSD (6.0%), TOF (4.7%), COA (3.4%), AS (3.0%), and TGA (1.9%)
Down Syndrome as a risk factor					
Alabdulgader (2001)	740 CHD cases	Hospital	1997-2000	-	VSD was the most common defect (39.5%), followed by ASD (11.5%), PS (8.9%), PDA (8.6%), AVSD (3.5%), TOF (4.2%), COA (2.7%), AS (3.5%). DS patients with CHD presented with higher proportion of non-cyanotic lesions (VSD-30%, AVSD -25%, PDA -20%, ASD-16%), than cyanotic lesions (TAPV -5%, TOF -4%).
Abbag (2006)	98 DS cases	Hospital	1994-2005	-	VSD being the most common (33.3%) followed by AVSD (22.8%), ASD (21.1%), PDA (14%) and TOF (5.3%). Sixteen patients (16.3%) died at a mean age of 19 months of which 15 of them (93.8%) had anomalies.
Al-Jarallah (2009)	110 DS cases	Hospital	2001-2004	-	Incidence of CHD in DS was 49%, the incidence of VSD was the highest (43%), followed by ASD (25%), AVD (15%), PDA (7%), and finally TOF (4%).
Al-Mesned et al. (2012)	316 DS cases	Hospital	2008-2010	5.4 /1,000 live birth (incidence)	VSD was the most common lesion (22.5%), COA (14.9%), AVSD (8.5%), PS (7.6%), and TOF (5.7%). 15% of the subjects suffered from other syndromes of which DS was the most common (14.2%).

Table 1. Cont'd.

Al-Aama et al. (2012)	130 DS cases	Hospital	2007-2011	7.1 per 1,000 live births	86.8 % children with DS had CHD. PDA (47.8%), followed by ASD (41.3%), trivial tricuspid regurge (33.7%), VSD (29%), and PFO (28.3%).
Consanguineous marriage as a risk factor					
Al-Abdulkareem and Ballal (1998)	-	PHCC and the Maternity and Children's Hospital	1998	-	No significant differences between children of consanguineous and non-Consanguineous marriages with respect to rates of inherited diseases and reproductive wastage.
Becker and Halees (1999)	949	Congenital Heart Disease Registry	1998	-	The prevalence of CHD which was significantly higher among first-cousin marriages (41.6%) as compared to the general population (28.4%). Down's syndrome was found in 49 patients (5.2%) with 23 from consanguineous marriages.
Seliem et al. (2007)	37 families	Hospital	1996-2000	-	Consanguineous marriages resulted in twenty-three of these families (62%). The prevalence of dilated cardiomyopathy was considerably higher between consanguineous cases; 26 vs. 2 in non-consanguineous marriages
El Mouzan et al. (2008)	11554	Community-based survey	2004-2005	-	56% of the respondents were in consanguineous marriages and CHD to be the only statistically significant disease associated with first cousin consanguinity
Becker (2012)	891	Congenital Heart Disease Registry		-	Consanguinity was significantly higher in the sample (40.4%) compared to the general population (28.4%). Consanguinity was found to be significantly associated with some types of CHD such as VSD, ASD, AVSD, PA, and PS while no significant relationship was found with TOF, TA, AS, COA, and PDA
Diabetic Mothers					
Abu-Sulaiman and Subaih (2004)	100	Hospital	2000-2001	-	Incidence of CHD in children of diabetic mothers was determined to be higher than in the general public; 150 per 1,000 live births, (after excluding PDA and hypertrophic cardiomyopathy). The predominant lesions were PDA (70%) followed by PFO (68%), HCMF (38%), ASD (5%), VSD (4%), MVP (2%)
Maternal Obesity					
Khalil et al. (2008)		Registry data	1998-2005	-	No significant association in incidence of CHD and maternal obesity
Social Impact					
Almesne et al. (2013)	41 parents	Hospital	2011-2012	-	Families of children with complex CHD had significantly higher IFS score, 62 vs. 51 (p=0.005) with a significant difference in both the family impact and mastery domains
Fetal outcome					
Bader et al. (2013)	-	Hospital-based database	2002-2012		Overall mortality rate for fetuses with AVSD was 48%. Extra-cardiac anomalies are an independent risk factor for prediction of mortality.

VSD: Ventricular Septal Defect, ASD: Atrial Septal Defect, PS: Pulmonary Stenosis, PDA: Patent DutusArteriosus, AVSD: Atrio-ventricular Septal, TOF: Tetralogy of Fallot, AS: Atrial Stenosis CoA: Coarctation of Aorta, TGA: Transposition of the Great Arteries, IFS: Impact on Family Scale, and DS: Down syndrome.

prevalence of CHD among DS patients (Al-Jarallah, 2009). Al-Aama et al. (2012) described the prevalence of CHD among DS patients in a prospective hospital-based study conducted between 2007 and 2011. A total of 130 DS patients aged 0 to 33 years (mean 5 ± 4.9) were included. The results found CHD in 86.8% of the patients with a prevalence of 7.1 per 1,000 live births (Al-Aama et al., 2012). Abbag et al., in 2006 documented that CHDs was found in 61.3% of DS patients (Abbag, 1998). Al Massned et al., found that DS is the most commonly encountered syndrome among children with CHD (Al-Mesned et al., 2012).

Consanguineous marriage

Al-Abdulkareem and Ballel, (1998) documented a non-significant difference for rates of inherited diseases between families of consanguineous and non-consanguineous marriages (Al-Abdulkareem and Ballel, 1998). Becker and Al Halees (1999) studied the relationship between CHD and consanguineous marriages (Becker and Al Halees, 1999). First-cousin marriages among families of children with CHD (41.6%) were significantly higher than that in the general population (28.4%) (Becker and Al Halees, 1999). Becker et al. (2001) documented the prevalence of various CHD lesions in patients who were the product of first-cousin marriages and found consanguinity was significantly higher in the sample (40.4%) compared to the general population (28.4%). Consanguinity was found to be significantly associated with some types of CHD (Becker et al., 2001). Seliem et al., (2006) investigated the influence of consanguinity on the pattern of familial aggregation in CHD. Consanguineous marriages resulted in twenty three of these families (62%) (Seliem et al., 2006). El Mouzanet et al. (2008) observed the role of consanguinity in genetic disorders and found that 56% of the respondents were in consanguineous marriages and that CHD to be the genetic disease most significantly associated with first cousin consanguinity (EIMouzan et al., 2008).

Diabetes and obesity

Abu-Sulaiman and Subaih, (2004) used a prospective cohort to investigate the relationship between CHD and insulin dependent diabetic mothers. Incidence of CHD in children of diabetic mothers was determined to be higher than in the general public; 150 per 1,000 live births (Abu-Sulaiman and Subaih, 2004). Khalil et al. (2008) conducted a retrospective study and documented no significant association in incidence of CHD and maternal obesity.

Impact and mortality studies

Almesned et al. (2013) measured the social impact of CHD on families of children with a complex CHD. Results showed that families of children with complex CHD had significantly higher Impact of Family Scale (IFS) score, 62 vs. 51 ($p = 0.005$) with a significant difference in both the family impact and mastery domains (Almesned et al, 2013). Bader et al. (2013) evaluated risk factors for prediction of outcome in fetal of AVS defect through retrospective design documented that overall mortality was 48% for fetus with AVSD (Baderet al., 2013).

DISCUSSION

There were 21 articles included in the review. Of those, the prevalence of CHD in Saudi Arabia was addressed in two studies. Alqurashi et al. (2006) conducted a community-based national prevalence study and reported approximately 21 cases per 10,000 persons. While Greer et al. (2005) and Alqurashi et al. (2006) used the CHD registry of KFSH and found it to be three fold at 74.8 per 10,000 persons. International studies have reported prevalence rates ranging from 10 to 119 per 10,000 persons (Samánek et al., 1989; Marelli et al., 2007; Dolk et al., 2010; Koshnood et al., 2010; van der Bom et al., 2012). Various factors may contribute to the differences in prevalence and relative frequencies of CHD between these studies including the study setting. Hospital based studies, for example, will often report a higher prevalence than community based studies due to the higher relative frequency of VSD, the most common type of CHD, which often closes spontaneously in early childhood and would not be detected in most studies outside of the hospital. In addition, minor forms of CHD, such as small PDA and ASD, may go undetected outside of hospital settings due to their subtle clinical signs. On the other hand, children with severe forms of CHD may die before one year of age thus reducing prevalence in community based studies. Nonetheless while the study methodology must be taken into consideration when making any comparisons, community based studies in China and India have reported higher prevalence's of 50 and 42 per 10,000 persons, respectively than that conducted in Saudi Arabia (Chadha et al., 2001; Jiang et al., 2005). Another important factor is the definition used for CHD as some studies excluded structural abnormalities that were not of functional significance (Abbag, 2006; Alqurashi et al., 2006; Alnajjar et al., 2009; Almawazini and Al-Ghamdiin, 2011).

Bhat et al. (1997) for example, did not exclude ASD in neonates and reported a relative frequency of 26% while in other studies in Saudi Arabia they ranged from 8.5 to 11.5% (Baht et al., 1997). The sensitivity of the diag-

nostic tools used is another factor affecting detection rates of CHD between studies as echocardiography was used in all studies in Saudi Arabia but was not available in previously conducted international studies. The most common cardiac congenital lesion reported in KSA was VSD ranging from 29.5 to 39.5% which is consistent with other parts of the world (Rose et al., 1964; Hoffman et al., 2004; Koshnood et al., 2010). The order of frequency of other forms of CHD however is less consistent. The second most common type of CHD in Kingdom of Saudi Arabia was ASD, which was the second most frequently reported disorder in terms of incidence in the US, Canada and Bohemia while other studies found it to be less common; the fourth most common form in Hungary at 10.4% and the fifth most common type in Sweden at 4.3% (Rose et al., 1964; Mitchell et al., 1971; Mészáros et al., 1975; Samánek et al., 1989; Sípek et al., 2010).

Variation in frequencies has been attributed to methodology and sensitivity of diagnostic tools, particularly as older studies have not used echocardiography, which was used in all of the studies in KSA. The cause of congenital heart disease is largely multifactorial and occurs through a combination of genetic and environmental factors. However, the role of chromosomal abnormality is conspicuous with approximately 20% of cases attributed to chromosomal anomalies (Blue et al., 2012). The association of CHD with DS was first described by Evans in 1950 (Carlgrén, 1959). Since then a number of studies have consistently shown an association between the two conditions (Evans, 1950; Granzotti et al., 1995; Wells et al., 1994; de Rubens Figueroa et al., 2003; Vida et al., 2005; Roizen et al., 2014). As CHD is the greatest cause of death in infants and young children with DS, describing the prevalence and types of defects found in DS is relevant in facilitating early intervention and appropriate management (Evans, 1950).

Presence of CHD in children with Down's Syndrome in central KSA was reported as 49% while in the Southwest region where CHD is more prevalent, it was higher (61%) (Abbag, 1998 and Al-Jarallah, 2009). Al-Aama et al. (2012) reported a greater prevalence of 86.6%, possibly due to the study being conducted from a genetic referral center. International studies ranged from 40 to 55% (Evans, 1950; Wells et al., 1994; de Rubens Figueroa et al., 2003; Vida et al., 2005; Al-Aama et al., 2012; Roizen et al., 2014). Similar to CHD in the general population, VSD was the most common lesion in DS, which is also consistent with most international studies (Abbag F, 1998; Al-Jarallah, 2009 and Al-Aama et al., 2012). Relative frequency of other types of CHD, however, varied among the studies due in part to the variation in method used for categorization. For example when multiple types of CHD were detected, Al-Jarallah

(2009) reported only on the dominate one while Al-Aama (2012) reported on them both in isolation or in combination, therefore PDA, for example, was only 7% in the former and 47.8% in the latter. The role of consanguinity in recessive diseases is well known, however, its potential role in certain common birth defects is unclear. Most studies support the view that consanguineous marriages increase susceptibility of CHD, particularly at first cousin level (Shieh et al., 2012). This is particularly the significant as consanguineous marriages are common in Saudi Arabia (Al Husain and Al Bunyan, 1997; Al-Abdulkareem et al., 1998 and Shieh et al., 2012).

Prevalence of consanguineous marriages was found to be as high as 51% in Riyadh, 47 and 52% in the Eastern province (Al-Abdulkareem and Ballal, 1998). El-Hazmi screened 3212 families in all regions of KSA and found 57.7% were consanguineous with first cousin marriage the most common type (28.4%) (El-Hazmi et al., 1995). In Kingdom of Saudi Arab first cousin marriages were significantly associated with VSD, ASD, AVSD, PS, and PA (Becker et al., 2001). Similarly, septal defects (VSD and ASD) were consistently found to be associated with consanguinity especially at first cousin level, in several international studies (Shieh et al., 2012). The less common forms of CHD with lower incidence (AVSD, PS, PA) may not have achieved enough power to determine the effect of consanguinity in international studies and may require large population based trials to accurately determine this relationship. The relationship of DM and CHD has been well established in Type 1, Type 2 and gestational DM (El-Hazmi et al., 1995; Narchi and Kulaylat, 2000 and Schaefer-Graf et al., 2000). Loffredo found a strong association between maternal diabetes and CHD (OR = 4.7, 95% CI 2.8 to 7.9) with all-cause mortality of children with CHD more than double in diabetic mothers than in non-diabetic (39 and 17%, respectively) (Loffredo et al., 2010). Similarly, Lukas A. also had identified a strong association of CHD and the offspring of diabetic mothers (p -value < 0.05) (Lisowski et al., 2010). Schaefer-Graf et al., (2000) reviewed 4,180 pregnancies complicated by gestational or type 2 DM and found the initial fasting serum glucose levels were significantly higher in the mothers of children born with anomalies.

The most common major anomalies were cardiac (37.6%) (Schaefer-Graf et al., 2000). Narchi and Kulaylat, (2000) estimated that CHD occurs in 5% of infants born to diabetic mothers with the highest relative risk for major defects occurring in mothers with gestational diabetes and developing insulin resistance in the 3rd trimester (Narchi and Kulaylat, 2000). In Saudi Arabia, Abu-Sulaiman and Subaih (2004) reported incidence of CHD in mothers with insulin dependent DM as 150 per 1,000 live births. This is significantly higher than the incidence

reported in the general population (2.1 to 10.7 per 1,000 live births) (Greer et al., 2005; Alqurashi et al., 2006). The detection and inclusion of minor forms of CHD may have contributed to this higher incidence. The limitations of this review includes limiting our search for articles in English. However, most if not all studies by research institutes and universities are in English in the Arab world. We might have missed some articles as we did not search into different databases like KoreaMed and Embase but local journals were reviewed to include all the study related to the Saudi Arabia. Publication bias, which is the tendency for publishing manuscripts positive finding is a potential limitation of all systematic reviews including our review, and certainly might explain, partially the significant association between CHD and some factors like maternal diabetes and advanced age. Limitations of this systematic review derive also from limitations of the individual studies included. Most of the studies conducted in Saudi Arabia were cross-sectional with an aim of characterizing patients diagnosed with CHD in terms of defect type or associated factors with very few follow-up studies that aims to know the prognosis, burden and consequences of these conditions on the society and healthcare services.

CONCLUSION

The results of this systematic review give a general understanding of the CHD epidemiology in Saudi Arabia. These diseases, that pose a considerable impact on children and their families, have higher prevalence than that in Western countries and comparable to those reported in other developing countries. Consanguineous marriages, maternal age, diabetes and Down syndrome and were among risk factors related to CHD in studies conducted in Saudi Arabia. Identified risk factors are potentially modifiable, emphasizing the importance of public health programs that are aimed at tackling such determinants. Studies that explored the prognosis and burden of these diseases on the Saudi society and healthcare services are scarce and should be the focus for future research.

Conflict of interest

The authors declare that they have no conflicts of interest.

REFERENCES

Abbag F (1998). Pattern of congenital heart disease in the Southwestern region of Saudi Arabia. *Ann. Saudi Med.* 18:393-395.

- Abbag FI (2006). Congenital heart diseases and other major anomalies in patients with Down syndrome. *Saudi Med. J.* 27(2):219-222.
- Abu-Sulaiman RM, Subaih B (2004). Congenital heart disease in infants of diabetic mothers: echocardiographic study. *Pediatr. Cardiol.* 25(2):137-140.
- Al-Aama JY, Bondagji NS, El-Harouni AA (2012). Congenital heart defects in Down syndrome patients from western Saudi Arabia. *Saudi Med. J.* 33(11):1211-1215.
- Alabdulgader AA (2001). Congenital heart disease in 740 subjects: Epidemiological aspects. *Ann. Trop. Paediatr.* 21(2):111-118.
- Al-Abdulkareem AA, Ballal SG (1998). Consanguineous marriage in an urban area of Saudi Arabia: rates and adverse health effects on the offspring. *J. Commun. Health* 23(1):75-83.
- Al Husain M, Al Bunyan M (1997). Consanguineous marriages in a Saudi population and the effect of inbreeding on prenatal and postnatal mortality. *Ann. Trop. Paediatr.* 17(2):155-60.
- Al-Jarallah AS (2009). Down's syndrome and the pattern of congenital heart disease in a community with high parental consanguinity. *Med Sci. Monit.* 15(8):409-412.
- Almawazini AM, Al-Ghamdi AS (2011). Congenital heart disease in south-west Saudi Arabia. *Saudi Med. J.* 32(2):195-196.
- Almesned SA, Al-Akhfash A, Mesned AA (2013). Social impact on families of children with complex congenital heart disease. *Ann. Saudi Med.* 33(2):140-143.
- Al-Mesned A, Al Akhfash AA, Sayed M (2012). Incidence of severe congenital heart disease at the province of Al-Qassim, Saudi Arabia. *Congenit Heart Dis.* 7(3):277-282.
- Alnajjar AA, Morsy MF, Almuzainy IS, Sheikh AA (2009). Pediatric heart diseases in Madina, Saudi Arabia. Current status and future expectations. *Saudi Med J.* 30(9):1186-1191.
- Alqurashi M, ElMouzan M, Al Herbish A (2006). Symptomatic congenital heart disease in the Saudi Children and Adolescents. *Project. Ann. Saudi Med.* 27(6):442-444.
- Bader RS, Punn R, Silverman NH (2013). Evaluation of Risk Factors for Prediction of Outcome in Fetal Spectrum of Atrioventricular Septal Defects. *Congenit Heart Dis.* 9(4):286-293.
- Baht BA, Sheikh A, Khan A, Dad MAI (1997). Pattern of congenital heart disease among children in Madina Munawara. *J. Saudi Heart Assoc.* 9:16-19.
- Becker S, Al Halees Z (1999). First-cousin matings and congenital heart disease in Saudi Arabia. *Community Genet.* 2(2-3):69-73.
- Becker SM, Al Halees Z, Molina C, Paterson RM (2001). Consanguinity and congenital heart disease in Saudi Arabia. *Am. J. Med. Genet.* 99(1):8-13.
- Bernier PL, Stefanescu A, Samoukovic G, Tchervenkov CI (2010). The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. *Semin. Thorac. Cardiovasc. Surg. Pediatr. Cardiol. Surg. Annu.* 13(1):26-34.
- Blue GM, Kirk EP, Sholler GF, Harvey RP (2012). Congenital heart disease: current knowledge about causes and inheritance. *Med. J. Aust.* 197(3):155-159.
- Carlgen LE (1959). The incidence of congenital heart disease in children born in Gothenburg 1941-1950. *Br. Heart J.* 21(1):40-50.
- Chadha SL, Singh N, Shukla DK (2001). Epidemiological study of congenital heart disease. *Indian J. Pediatr.* 68(6):507-510.
- de Rubens Figueroa J, del PozzoMagaña B, PablosHach JL, Calderón Jiménez C, CastrejónUrbina R (2003). Heart malformations in children with Down syndrome. *Rev. Esp. Cardiol.* 56(09):894-899.
- Dolk H, Loane M, Garne E (2010). The prevalence of congenital anomalies in Europe. *Adv. Exp. Med. Biol.* 686:349-364.
- El-Hazmi M, Al-Swailem AR, Warsy AS, Al-Swailem AM, Sulaimani R, Al-Meshari AA (1995). Consanguinity among the Saudi Arabian population. *J. Med. Genet.* 32(8):623-626.
- El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA (2008). Consanguinity and major genetic disorders

- in Saudi children: A community-based cross-sectional study. *Ann. Saudi Med.* 28(3):169-173.
- Evans PR (1950). Cardiac anomalies in mongolism. *Br. Heart J.* 12(3):258-262.
- Granzotti JA, Paneto IL, Amaral FT, Nunes MA (1995). Incidence of heart defects in Down syndrome. *J. Pediatr. (Rio J).* 71(1):28-30.
- Greer W, Sandridge AL, Al-Menieir M, Al Rowais A (2005). Geographical distribution of congenital heart defects in Saudi Arabia. *Ann. Saudi Med.* 25(1):63-69.
- Hoffman JIE, Kaplan S, Liberthson RR (2004). Prevalence of congenital heart disease. *Am. Heart J.* 147(3):425-439.
- Jaiyesimi F, Ruberu DK, Misra VK (1993). Pattern of congenital heart disease in King Fahd Specialist Hospital, Buraidah. *Ann. Saudi Med.* 13(3):407-411.
- Jiang LH, Duan CQ, Ma ZQ, Zhu LJ, Yin WJ, Zou HL, Li P, Wu J, Wei J, Na ZH, Chen WM (2005). Epidemiological investigation on congenital heart disease in several regions of Yunnan province. *Zhonghua Liu Xing Bing Xue Za Zhi* 26(3):182-186.
- Khalil HS, Saleh HS, Shazia, Subhani N (2008). Maternal obesity and neonatal congenital cardiovascular defects. *Int. J. Gynaecol. Obstet.* 102(3):232-236.
- Koshnood B, Lelong N, Houyel L, Thieulin AC (2010). Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. *Heart* 98(22):1667-1673.
- Lisowski LA, Verheijen PM, Copel JA, Kleinman CS, Wassink S, Visser GH, Meijboom EJ (2010). Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. An international clinical collaboration, literature review, and meta-analysis. *Herz.* 35(1):19-26.
- Loffredo CA, Wilson PD, Ferencz C (2010). Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. *Teratology* 64(2):98-106.
- Marelli AJ, Mackie AS, Ionescu-Iltu R, Rahme E, Pilote L (2007). Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation* 115(2):163-172.
- Mészáros M, Nagy A, Czeizel A (1975). Incidence of congenital heart disease in Hungary. *Hum. Hered.* 25(6):513-519.
- Mitchell SC, Korones SB, Berendes HW (1971). Congenital heart disease in 56,109 births. Incidence and natural history. *Circulation* 43(3):323-332.
- Narchi H, Kulaylat N (2000). Heart disease in infants of diabetic mothers. *Images Paediatr. Cardiol.* 2(2):17-23.
- Roizen NJ, Magyar CI, Kuschner ES, Sulkes SB, Druschel C, van Wijngaarden E, Rodgers L, Diehl A, Lowry R, Hyman SL (2014). A community cross-sectional survey of medical problems in 440 children with Down syndrome in New York State. *J. Pediatr.* 164(4):871-875.
- Rose V, Boyd AR, Ashton T (1964). Incidence of congenital heart disease in children in the city of Toronto. *CMAJ* 91(3):95-100.
- Samánek M, Slavík Z, Zborilová B, Hroboňová V, Vorísková M, Skovránek J (1989). Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. *Pediatr. Cardiol.* 10(4):205-211.
- Schaefer-Graf UM, Buchanan TA, Xiang A, Songster G, Montoro M, Kjos SL (2000). Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am. J. Obstet. Gynecol.* 182(2):313-20.
- Seliem MA, Bou-Holaigah IH, Al-Sannaa N (2006). Influence of consanguinity on the pattern of familial aggregation of congenital cardiovascular anomalies in an outpatient population: studies from the eastern province of Saudi Arabia. *Community Genet.* 10(1):27-31.
- Shieh J, Bittles A, Hudgins L (2012). Consanguinity and the Risk of Congenital Heart Disease. *Am. J. Med. Genet. A.* 158(5):1236-1241.
- Sípek A, Gregor V, Sípek A Jr, Hudáková J, Horáček J, Klaschka J, Langhammer P, Petrzilková L, Klímová B, Perinová B, Wiesnerová J (2010). Incidence of congenital heart defects in the Czech Republic, Current data. *Ceska Gynekol.* 75(3):221-242
- van der Bom T, Bouma BJ, Meijboom FJ, Zwinderman AH, Mulder JM (2012). The prevalence of adult congenital heart disease: Results from a systematic review and evidence based calculation. *Am. Heart J.* 164(4):568-575.
- Vida VL, Barnoya J, Larrazabal LA, Gaitan G, de Maria Garcia F, Castañeda AR (2005). Congenital cardiac disease in children with Down's syndrome in Guatemala. *Cardiol Young* 15(03):286-290.
- Wells GL, Barker SE, Finley SC, Colvin EV, Finley WH (1994). Congenital heart disease in infants with Down's syndrome. *South Med. J.* 87(7):724-727.
- Wu MH, Chen HC Lu, Chun-Wei, Wang, Jou-Kou Huang, Shin-Chung Huang, San-Kuei (2010). Prevalence of congenital heart disease at live birth in Taiwan. *J. Pediatr.* 156(5):782-785.